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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/782,899	FUJIMORI ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/15/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *5,23,26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-21,24 and 25* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/816,391.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/23/04;6/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1-27 are pending.

The amendment to claims 12-21 and 24-25 in paper filed on 6/15/05 is acknowledged and considered by the examiner.

It is acknowledged that the election of species (DNA coding for a protein having an anti-tumor activity) was made in error in the response filed on 6/15/05. Applicant changing the elected species to DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance in the response filed on 6/15/05 is acknowledged by the examiner.

Election/Restrictions

Applicant's election with traverse of Group I and species (DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance) in the reply filed on 6/15/05 is acknowledged. The traversal is on the ground(s) that any search for the bacterium in Group I will certainly encompass references for the bacterium of the Group III claims, all of the claims are classified under 424 and it would not place an unnecessary burden on the examiner to search and examine Groups I and III, Group II is directed to a nucleotide sequence of the HU gene from Bifidobacterium, a search for the bacterium of Group III would also reveal sequence information pertaining to the nucleotide sequence as claimed in Group III. This is not found persuasive because a search for the genetically modified bacterium in Group I would not overlap with a bacterium in Group III because the bacterium in

Group III is not genetically modified. Even though Group I and III are classified in the same class the subclass for each group is different, which indicates that it would require a different search for each group. In addition, the applicant fails to address the examiner's reasons for separating Group III and Group I in the office action mailed on 5/16/05. The search for the bacterium in Group III does not require a sequence search, which is required for the sequence in Group II. In addition, the applicant failed to address the examiner's reasons for separating Group I, II, and III in the office action mailed on 5/16/05. The traversal against the species is on the ground(s) that examiner is requested to review MPEP 803.02, examination of all of the species at one time would not impose a serious burden on the examiner, there is a disclosure of relationship between the claimed species because the species code for proteins that affect tumors, the claims are not broken into separate classifications on the basis of which species is claimed and it can be assumed that the classification of all the claims into a single group was made considering each of the species such that the species of any species would be coextensive and include the remaining species. This is not found persuasive because although the examiner appreciates the applicants suggestion to review MPEP 803.02, the examiner has followed the guidelines in MPEP 800 (including 803.02) for requiring an election of species between the species in claim 4. There is not a relationship between the species in claim 4(a) and 4(b) because an interleukin-2 does not have the same activity of a precursor of an anti-tumor substance because a precursor of an anti-tumor substance requires an additional substance to activate the precursor and the interleukin-2 does not require a second substance to activate the protein. The precursor is inactive and cannot affect tumors, whereas a protein having anti-tumor activity can affect tumors and is active. The MPEP does not require that species be broken into separate

classifications. For the reasons set forth above, a search for a protein having an anti-tumor activity would not overlap with a search for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance. Thus, a search of all of the species would impose a serious search burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Upon further consideration of the amendment to claims 12-21 and 24-25, the claims are joined with the elected group.

Claims 23, 26, and 27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and DNA coding for a protein having antitumor activity in claim 4 and claim 5 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 6/15/05.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence(s) of the specification or in an application data sheet by identifying the prior application by application number (37 CFR 1.78(a)(2) and (a)(5)). If the prior application is a non-provisional application, the specific reference must also include the relationship (i.e., continuation, divisional, or continuation-in-

part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

The instant application is a CON of application 09/816,391 and a reference to this application with the current status of '391 is missing in the first line of the instant specification.

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/816,391, filed on 3/26/01.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 6/20/05 and 8/23/04 are being considered by the examiner.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See page 23.

Claim Objections

Applicant is advised that should claim 17 be found allowable, claim 18 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim 22 is objected to because of the following informalities: grammatical error in the format of the claim, suggest amending the claim to read -- A genetically modified bacterium, wherein the bacterium is a *Bifidobacterium longum* 105-A/pBLES100-S-eCD E having the deposit accession number FERM BP-7274 --. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-12, 14-19, 21, and 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for specifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, comprising administering a genetically modified bacterium to an individual with cancer, wherein the genetically modified bacterium is a *Bifidobacterium longum*, which comprises an expression vector comprising a DNA sequence coding for an anti-tumor protein, and does not reasonably provide enablement for a method for specifically delivering to tumor tissues under anaerobic conditions in an individual with cancer a genetically modified bacterium, wherein the genetically modified bacterium selected from the group consisting of a genus of *Bifidobacterium*. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The field of the invention is using a bacterium from the genus *Bifidobacterium* as a gene delivery vector comprising a gene used in a method of delivering the gene delivery vector to tumor tissues under anaerobic conditions.

The art of record for *Bifidobacterium* as exemplified by Yazawa et al. (Breast Cancer Research and Treatment, Vol. 66, pp. 165-170, 2001) teaches that:

> *Bifidobacterium* is non-pathogenic bacteria found in the intestine of human and some other mammalian animals. These organisms are believed to have health-promoting properties for their host, including increase of the immune response, inhibition of carcinogenesis, and protection of the host against viral infections. However, despite increasing attention to this bacterium in many fields, little is known about its genetic property (page 165).

Furthermore, the state of the art for transforming bacterium from the genus *Bifidobacterium* is highly unpredictable as exemplified by Argnani et al. (IDS, Microbiology, Vol. 142, pp. 109-114). Argnani teaches:

> Although electroporation technique has proven to be widely applicable to genetically transform bacterial strains, all Bifidobacterium so far examined have proved refractory to efficient and reproducible transformation (page 109).

Yazawa, whom teaches that, further supports this:

> To be able to exploit the potential of these organisms for cancer gene therapy, detailed knowledge is required about such basic biological phenomena as cellular metabolism, gene expression, protein secretion, and genetics. Yazawa further states that, studies on Bifidobacterium at the molecular level are severely limited in the absence of an efficient transformation. Recently, Matsumura and colleagues developed a system for convenient and reproducible genetic transformation of B. longum (page 169).

The applicants provide several working examples displaying the transformation of *Bifidobacterium longum* with a gene and the deliver of the genetically modified bacterium to tumor-bearing mice (pages 46-61). The delivery displayed that the bacterium specifically targeted the tumors (page 48). In addition, one example displays the production of a genetically modified bacterium comprising a cytosine deaminase (CD) gene and an example introducing the bacterium, which was specifically expressed only in tumor tissues under anaerobic conditions in tumor-bearing mice (pages 55-61). In view of the instant specification and the art of record for using *Bifidobacterium* as a gene delivery vector, the claimed invention is only enabled for producing and using the *Bifidobacterium longum* comprising a gene for use in specifically delivering to tumor tissues under anaerobic conditions in a mammal because the as-filed specification and the art of record do not provide sufficient guidance for one skilled in the art to reasonably extrapolate from using *Bifidobacterium longum* to using the genus *Bifidobacterium* without an undue amount of experimentation. The art of record display that studies on Bifidobacterium at the molecular level are severely limited in the absence of an efficient transformation. Therefore, the state of the art is considered unpredictable and the as-filed

specification does not provide sufficient guidance for one skilled in the art to make and/or use a representative number of bacterium from the genus *Bifidobacterium* as gene delivery vectors.

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed bacterium from the genus *Bifidobacterium* other than the *Bifidobacterium longum* can be genetically modified and used as a gene delivery vector, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid delivery method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

The court in Enzo 188 F.3d at 1374, 52 USPQ2d at 1138 states:

> It is well settled that patent applications are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. In re Vaeck, 947 F.2d 48, 496 & n.23. 30 USPQ2d 1438, 1445 &n23 (Fed. Cir. 1991)(citation omitted). Here, however, the teachings set forth in the specification provide no more than a "plan" or "invitation" for those of skill in the art to experiment...; they do not provide sufficient guidance or specificity as to how to execute that plan. See Fiers v. Revel. 984 F.2d.1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993); In re Wright, 999 F.2d...[1557], 1562, 27 USPQ2d...[1510], 1514. [Footnote omitted].

On this record, it is apparent that the specification provides no more than a plan or invitation in view of the art of record exemplifying the unpredictability of making and using the claimed species of *Bifidobacterium* (See Argnani), for those skilled in the art to further experiment with different species of claimed genus of *Bifidobacterium* so as to provide a therapeutic method of cancer gene therapy as intended by the as-filed specification at the time the invention was made. See also Genentech Inc. v. Novo Nordisk A/S, 108 F.3d 1361, 1366, 42, USPQ2d 1001, 1005 (Fed. Cir. 1997)

> ("Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the public to understand and carry out the invention.")

In view of the art of record and the lack of guidance provided by the specification; the specification does not provide reasonable detail for what protocols are required for successfully transfecting different species *Bifidobacterium*, and it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from the specification to the full breadth of the claimed invention. Therefore, the as-filed specification is not enabled for the full scope of the claimed invention.

Furthermore, with respect to claims 1-4, 6-12, 14-18 and 24-25 directed to treating a solid tumor or delivering a gene to tumor tissue under anaerobic conditions, the specification only provides sufficient guidance for treating a tumor in an individual with cancer. The breadth of the claimed methods encompasses targeting genetically modified *Bifidobacterium* to a solid tumor in any environment, including an individual with cancer and a solid tumor *in vitro*. The specification only teaches one skilled in the art how to use the method for targeting the bacteria to a tumor in an individual with cancer. The as-filed specification does not teach one skilled in the art how to use the claimed method wherein the tumor is not in an individual with cancer. The art of record is absent for using the claimed method on solid tumors *in vitro*. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

Furthermore, with respect to claims 1-4, 6-11, 14-18 and 24-25, the claims encompass a recombinant *Bifidobacterium* comprising a DNA not operably linked to a promoter. The specification provides sufficient guidance for one skilled in the art to make and use a

recombinant *Bifidobacterium longum* comprising a promoter operatively linked to a DNA encoding an anti-tumor protein. However, the specification fails to provide sufficient guidance or evidence for one skilled in the art to make and use a recombinant *Bifidobacterium longum*, comprising a promoter that is not operatively linked to any specific nucleotide sequence. The teachings in the specification are directed to using a promoter to express an anti-tumor gene product. The as-filed specification provides sufficient guidance or factual evidence for how to make and use *Bifidobacterium longum* comprising a promoter operatively linked to DNA to direct DNA expression, however the claims do not recite such a structural limitation. Thus, to the extent the claims fail to recite distinguishing features to commensurate with the level of guidance presented, the claims are not considered enabled.

In addition, with respect to claims 1-3, 8-12, 16, 19, 24 directed to treating a solid tumor or delivering a genetically modified bacterium to tumor tissues under anaerobic conditions, the claimed method encompasses using a DNA encoding a protein with/without anti-tumor activity. The specification provides sufficient guidance or evidence for one skilled in the art to use a DNA encoding a protein with anti-tumor activity, but does not provide sufficient guidance for one skilled in art to reasonably correlate from using a protein with anti-tumor activity to the full scope of the claimed method encompassing using any protein without anti-tumor activity (e.g. Factor VIII, dystrophin, HIV, etc.). Thus, the claimed method is only enabled for using a DNA encoding a protein having anti-tumor activity and not for the full breadth of the claimed method.

In conclusion, the as-filed specification and claims coupled with the art of record at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable a method for specifically delivering to tumor tissues under anaerobic conditions in an

individual with cancer a genetically modified bacterium, wherein the genetically modified bacterium is a *Bifidobacterium longum*, which comprises an expression vector comprising a DNA sequence coding for a protein. Given that efficiently transfecting a representative number of *Bifidobacterium* was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to how to reasonably correlate efficiently transfecting *Bifidobacterium longum* to the other species of *Bifidobacterium* cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicants' disclosure and the unpredictability of transfecting *Bifidobacterium*.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-4, 6-20, and 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4, 6-15, and 24-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: delivering a recombinant *Bifidobacterium* comprising a DNA encoding a protein to a tumor tissue under anaerobic condition to an individual with cancer. The active steps to complete the methods are missing from the claims.

The phrase "is used as" in claims 1-3 (and claims dependent therefrom) is a relative term, which renders the claim indefinite. The phrase "is used as" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of

ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claims do not define the metes and bounds of the phrase. The claims do not define the term "used" and what way the gene delivery vector is used.

Claims 1-3 (and claims dependent therefrom) are vague and indefinite for failing to define the metes and bounds of the claims. It is unclear what subject matter the claims define. For example, the term "system" in claims 1-3 is a relative term, which renders the claim indefinite. The term "system" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In addition, it is not apparent whether the phrase "delivering DNA specifically to tumor tissues under anaerobic conditions" is referring to the gene delivery vector or the DNA.

The phrase "has a higher activity than it parent strain" in claim 2 (and claims dependent therefrom) is a relative term, which renders the claim indefinite. The phrase "has a higher activity than its parent strain" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bounds of the phrase. Since a parent strain is considered a wild type strain and does not endogenously express an anti-tumor gene, it is not apparent how the wild type strain can express an anti-tumor protein. Therefore, it is not apparent to one skilled in the art how you can compare expression of an anti-tumor protein in a bacterium that does not express the anti-tumor protein with a genetically modified bacterium that expresses the anti-tumor protein.

Claims 4, 7, 14, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: administering a precursor of an anti-tumor substance to a tumor tissue. The DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance requires the administration of a precursor for the DNA to perform its function in a tumor tissue.

The phrase "use of the bacterium as claimed in any one of claims 1-3" in claim 14 is a relative term, which renders the claim indefinite. The phrase "use of the bacterium as claimed in any one of claims 1-3" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The claim does not define the metes and bounds of the phrase because the claim does not define the term "used" and what way the bacterium is used. In addition, claims 1-3 are directed to a method and not a product.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the bacterium comprising a gene coding for a protein having the activity of converting a precursor of an anti-tumor substance into the anti-tumor substance.

Claims 16-20 recite the limitation "the bacterium as claimed in any one of claims 1 to 3". There is insufficient antecedent basis for this limitation in the claim. Claims 1-3 are directed to a method and none of the claims are directed to a bacterium.

The phrase "use of the method as in any one of claims 1 to 3" in claim 24 is vague as to how the method of claims 1 to 3 is used. Suggest amending claim 24 as follows: -- The method of any one of claims 1 to 3, wherein the tumor tissues are solid tumors --.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: administering a DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance. The precursor requires the administration of the DNA to perform its function in a tumor tissue.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The intended use of the bacterium (pharmaceutical composition) in the instant claims 16-20 has very little patentable weight for prior art rejections. See MPEP 2111.02. An intended use does not provide a structural difference between the claimed invention and a recombinant *Bifidobacterium* in the prior art.

Claims 1-3, 8, 9, 12, 14, 16, 19, 21, and 24 are rejected under 35 U.S.C. 102(a) as being anticipated by Yazawa et al (AJ). Yazawa teaches using a genetically engineered

Bifidobacterium longum comprising an expression vector comprising a gene coding for spectomycin adenyltransferase in a method of delivering the bacterium to solid tumor tissues in a mouse (abstract and pages 269-271).

Claims 1-4, 8, 9, 12, 14, 16-19, 21, and 24-25 are rejected under 35 U.S.C. 102(a) as being anticipated by Babincova et al. (AW). Babincova teaches introducing a gene encoding a luciferase into the genome of *Bifidobacterium longum* and using the genetically modified bacteria comprising the luciferase gene in a method of destroying neoplastic cells (pages 3-4). Babincova further teaches that *Bifidobacterium longum* is a nonpathogenic bacterium that selectively grows in hypoxic regions of tumors after systemic application (abstract).

Claims 16, 19, and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Matsumura et al. (AM). Matsumura teaches a *B.longum* comprising a shuttle vector (page 1211-1212).

Claims 1-3, 8, 12, 14, 15, 16, 19, 21, and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999). Yazawa teaches using Bifidobacterium longum as a gene delivery vector for treating cancer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-9, 17, 18, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999) taken with Brown (AC). Yazawa teaches using Bifidobacterium longum as a gene delivery vector for treating cancer. However, Yazawa does not specifically

teach introducing a DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into a tumor using *Bifidobacterium longum*.

However, at the time the invention was made, introducing a DNA coding for a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into a tumor using a genetically modified bacterium was well known to one of ordinary skill in the art as exemplified by Brown (columns 1-26). Brown teaches using a genetically modified bacterium to deliver an enzyme to the hypoxic/necrotic environment of a tumor and systemically administering a pro-drug, which is converted at the site of the tumor to the toxic agent by the enzyme (columns 25-26). The enzyme/prodrug combination can be selected from following: nitroreductase/CB1954; cytosine deaminase/5-fluorocytosine; beta-glucuronidase/glucuronidated anticancer drugs (columns 5-6).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa taken with Brown, namely to use a genetically modified *Bifidobacterium longum* comprising a nucleic acid sequence encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance in a method to treat tumor tissues under anaerobic conditions. One of ordinary skill in the art would have been motivated to introduce the DNA encoding a protein having an activity of converting a precursor of an anti-tumor substance into the anti-tumor substance into tumor tissues under anaerobic conditions using the genetically modified bacterium because the bacterium is a nonpathogenic anaerobic bacterium, which can selectively localize to solid tumors in an individual after systemic application and pro-drug cancer therapy was well known to one of ordinary skill in the art for treating tumor tissue.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa taken with Brown, namely to use any enzyme/prodrug combination in the method to treat tumor tissues under anaerobic conditions. One of ordinary skill in the art would have been motivated, as a matter of designer's choice, to use an enzyme/prodrug combination selected from following: nitroreductase/CB1954; cytosine deaminase/5-fluorocytosine; beta-glucuronidase/glucuronidated anticancer drugs because the enzyme/prodrug combinations were well known to one of ordinary skill in the art for treating hypoxic tumor tissue.

In addition, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Yazawa taken with Brown, namely to use an expression vector that has a promoter and terminator that function in a Bifidobacterium. One of ordinary skill in the art would have been motivated to use a promoter and terminator that function in the Bifidobacterium because one of ordinary skill in the art understands that a promoter and a terminator are required for the vector to express the protein of interest.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Claims 1-3 and 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yazawa et al. (Proceedings of the American Association for Cancer Research Annual Meeting, Vol. 40, pp. 88, 1999) taken with Brown (AC) as applied to claims 1-4, 6-9, 17, 18, and 25 above, and further in view of Blanche et al. (US 6518062).

Yazawa and Brown do not specifically teach using the enzyme/prodrug combination herpes simple virus type 1 thymidine kinase (HSV-1TK)/ganciclovir in the method of treating tumor tissue.

However, at the time the invention was made, introducing a vector comprising DNA coding for HSV type 1 thymidine kinase to tumor tissue and administering ganciclovir to tumor tissue was well known to one of ordinary skill in the art as exemplified by Blanche (columns 1-8). Blanche teaches using HSV-1TK and ganciclovir in a method of treating cancer cells (column 2).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Yazawa and Brown in further view of Blanche, namely to use any enzyme/prodrug combination in the method to treat tumor tissues under anaerobic conditions. One of ordinary skill in the art would have been motivated, as a matter of designer's choice, to use the enzyme/prodrug combination (herpes simplex virus type 1 thymidine kinase/ganciclovir) because the enzyme/prodrug combination was well known to one of ordinary skill in the art for treating tumor tissue as exemplified by Blanche (columns 1-8).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

The Declaration Deposit under the Budapest Treaty for *Bifidobacterium longum* 105-A/pBLES100S-eCD (FERM BP7274) is located in the parent application 09/816,391.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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